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RESEARCH**

APPLICATION NUMBER:

022454Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

<u>NDA:</u>	22-454
<u>Submission Date:</u>	November 16, 2010
<u>Category:</u>	1S
<u>Brand Name:</u>	DaTscan
<u>Formulations:</u>	Sterile Solution
<u>Route of Administration:</u>	Intravenous Bolus Injection
<u>Dosing Regimen:</u>	3-5 mCi
<u>Indication:</u>	Dopamine transporter imaging agent
<u>Sponsor:</u>	GE HealthCare, Inc.
<u>Type of Submission:</u>	New NDA (resubmission)
<u>Reviewer:</u>	Christy S. John, Ph.D.
<u>Team Leader:</u>	Young Moon Choi, Ph.D.
<u>Dates of Review:</u>	
	Received for Review: November 20, 2010
	First Draft: January 3, 2011

SYNOPSIS:

This resubmission of NDA 22-454, describes the sponsor's responses to the complete response letter issued by the Agency 12/23/2009. The resubmission contains the following: 1) an amended label with the requested controlled substance text, 2) a safety update, 3) a complete protocol for one of two separate PMC studies (to evaluate DaTscan image results agreement among non-Caucasian and Caucasian subjects), 4) a request for a proprietary name request, and 5) a request to be released from the PMC to study the effects of dopaminergic drugs on DaTscan results.

DaTscan (Ioflupane I-123 Injection) is a radiopharmaceutical containing [¹²³I]ioflupane, indicated for detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 5, had reviewed the original (submitted March 2009) submission and found it generally acceptable for approval from clinical pharmacology perspectives. However, it was pointed out at the OCP Briefing by this reviewer that the sponsor had not studied the effect of commonly used anti-Parkinson's drugs and various anti-depressants and dopaminergic drugs used by elderly patients. These drugs may have a potential to alter the DaTscan imaging results as shown in the literature.

It was discussed at the OCP Briefing that clinical studies have shown a decrease in striatal binding of 30-50% on patients with methamphetamine or d-amphetamine (appetite suppressant) (Am. J. Psychiatry 2001, 158, 377-382; Neuropsychopharmacol. 2007, 17, 46-52). Bupropion (an antidepressant and a smoking cessation agent) has been shown to cause a 20% decrease in striatal binding in depressed patients (J. Affect Disorder 2005, 89, 115-123). Single dose of 20 mg Citalopram (SERT blocking ligand) increased striatal binding ratio to 20% (J. Nucl. Med. 2007, 48, 359-366) with dopamine transporter (DAT) imaging with ¹²³I-FP-CIT (¹²³I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane) (an analog of DaTscan) SPECT when used to detect loss of nigrostriatal cells in parkinsonism.

The Complete Response letter of September 8, 2009 requested that GE Healthcare conduct a clinical trial to assess the impact of dopaminergic drugs (including levodopa/carbidopa) on DaTscan image results. In response, GE Healthcare submitted a proposed study design. Subsequently, GE Healthcare has reviewed the medical literature and consulted with outside experts and concluded that a clinical study would not provide additional information over what is already available.

This review focused on sponsor's new literature data and their request for justification of the release from the PMC to study the effects of dopaminergic drugs on DaTscan results.

The sponsor cited several recent literature studies in patients and in preclinical studies to justify the release from the PMC. Levodopa has no effect on DaTscan images assessed quantitatively, according to a report by Schillaci et al. (Schillaci O, Pierantozzi M, Filippi L, *et al.* The effect of levodopa therapy on dopamine transporter SPECT imaging with 123I-FP-CIT in patients with Parkinson's disease. *Eur J Nucl Med Mol Imaging*. 2005;32:1452–1456). Schillaci et al. studied the effects of levodopa on abnormal DaTscan images in 15 patients with Parkinson's disease of 24 to 80 (mean 48) months duration, whose only antiparkinson therapy was levodopa. The patients were imaged with DaTscan at baseline while on levodopa, and were re-imaged after a 20-day levodopa washout. Target-to-background signal ratios were determined for whole striata and its sub-regions (caudate, putamen). Changes in mean ratios ranged from +0.6% to -4.6%, and none was statistically significant,

The sponsor has cited other recent studies that have shown that neither levodopa nor the dopamine agonists pramipexole or pergolide affected [¹²³I]β-CIT SPECT images of dopamine transporter (DaT) binding. The lack of an effect of levodopa was predictable given the Schillaci findings and the similarity of [¹²³I]β-CIT and DaTscan with regard to chemical structure and mechanism of action. It is thus likely that the lack of effect of pramipexole and pergolide on [¹²³I]β-CIT SPECT will also apply to DaTscan.

The sponsor's response based on similar mechanism of action of [¹²³I]β-CIT SPECT and DaTscan appears reasonable for certain drugs such as levodopa, pramipexole and pergolide etc. However, the imaging results could be altered if patients are taking amphetamine, bupropion, norepinephrine etc. For this reason the Agency had recommended the following language, "DaTscan binds to dopamine transporters. Drugs that bind to the dopamine transporter with high affinity may interfere with the image obtained following DaTscan administration. These potentially interfering drugs consist of amoxapine, amphetamine, benztropine, bupropion, buspirone, cocaine, mazindol, methamphetamine, methyphenidate..... Whether discontinuation of these drugs prior to DaTscan administration may minimize the interference with DaTscan image is unknown. The impact of dopamine agonist and antagonists upon DaTscan imaging result has not been established" in the drug interaction section of the label.

The sponsor had agreed with the Agency on the label in this Section. Therefore, we recommend to leave this language in Drug Interaction Section as is and to release sponsor from the PMC to study the effects of dopaminergic drugs on DaTscan results.

RECOMMENDATION:

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 5, has reviewed the resubmission for NDA 20-454. The literature data shows that for some drugs (commonly taken by Parkinson's patients such as levodopa etc.), there may not be any effect of image results quality. For other drugs the interaction cannot be ruled out. The Agency has placed a language in drug-interaction study section in the label. The PMC therefore can be released.

Signature
Christy John, Ph.D.

Concurrence

Young M. Choi, Ph.D.



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
01/04/2011

YOUNG M CHOI
01/04/2011
I concur.

NDA	22-454	Submission Date	March 16, 2009
Brand Name	[¹²³ I]ioflupane or ¹²³ I-FP-CIT		
Generic Name	[I-123]DaTSCAN		
Reviewer	Christy S. John, Ph.D		
Team Leader	Young Moon Choi, Ph.D.		
OCP Division	V		
ORM Division	Division of Medical Imaging and Hematology Drug Products		
Sponsor	GE HealthCare Inc.		
Relevant IND(s)	None		
Submission Type; Code	P	1	
Formulation; Strength(s)	The clear and colorless solution supplied in single-use vials in which each milliliter contains 0.07 to 0.13 µg ioflupane, 74 MBq (2 mCi) of iodine-123 (as [123I]ioflupane) at calibration time, 5.7 mg acetic acid, 7.8 mg sodium acetate and 0.05 mL (5%) ethanol.		
Indication	Detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration		
Proposed Dose	3-5 mCi intravenous injection (less than 0.325 µg)		

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1 Executive Summary

The applicant (GE HealthCare Inc.) has submitted an NDA for the proposed indication of “detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.” The loss of nigrostriatal dopaminergic neurons is one of the anatomic hallmark of Parkinson’s Syndrome (PS) such as Parkinson’s Disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), etc. There is no disease detection claim in the proposed indication. This submission was granted a priority review based on an unmet medical need.

¹²³I-ioflupane (also called as DaTSCAN or iodine-123- 2-carbomethoxy- 3-(4-iodophenyl)-N-(3- fluoropropyl) nortropane or [¹²³I]FP-CIT in the submission) is a cocaine analog that binds dopamine transporter proteins (DAT). These proteins are located on presynaptic nigro-striatal terminal and are involved in dopamine reuptake.

In 2000, ¹²³I-FP-CIT was licensed as DaTSCAN in Europe to differentiate patients suffering from PS from essential tremor (ET). In 2006, ¹²³I-FP-CIT received additional registration for a new indication: to distinguish dementia with Lewy bodies (DLB) from Alzheimer’s disease (AD). ¹²³I-FP-CIT is now used in 32 European countries for these two indications.

Two clinical pharmacology studies and four clinical studies were submitted for the registration of product in US. Clinical pharmacology study CY96-FP2-CSR was a single centre, open study of an intravenous dopamine transporter ligand, containing 111 MBq (3 mCi) [¹²³I]FP-CIT, in healthy volunteers and patients with Parkinson’s disease to examine uptake kinetics in various brain sub regions. Another clinical pharmacology study CY95-FP.I was also a single center, open study of an intravenous injection containing 111 MBq [¹²³I]FP-CIT in healthy volunteers. The objective of the study was to investigate biodistribution and excretion characteristics of [¹²³I]FP-CIT in the whole body, and various organs as well as in blood and urine samples during the 48 hour period following intravenous injection containing approximately 111 MBq, and to calculate absorbed radiation dose estimates. These studies were reviewed.

1.1.1 Recommendations:

The Office of Clinical Pharmacology, Division of Clinical Pharmacology V has reviewed NDA 22-454. The application was found to be acceptable from a clinical pharmacology perspective provided that the applicant and the Agency come to a mutually satisfactory agreement regarding the language in the package insert. (See 3. Detailed Labeling Recommendations).

1.2 Phase IV Commitments: None

1.3 Summary of Clinical Pharmacology Findings:

Dose: The proposed radioactivity dose is 3-5 mCi to be injected intravenously, and the brain scan is recommended to start between three to six hours after injection of ^{123}I -ioflupane. This is based on the clinical experience and the doses reported in the published literature. No clinical dose finding studies were performed for this NDA. However, the sponsor demonstrated in a clinical pharmacology study that a dose of 3 mCi produced a high target (striatum) to non-target (occipital cortex, OCC) uptake to give a two-fold difference (at 3-6 hours) between healthy volunteers and PD patients.

Pharmacokinetics: DaTSCAN is administered intravenously. It is cleared rapidly from the blood after i.v. injection; only 5% of the administered activity remains in whole blood at 5 minutes post-injection. Uptake in the brain is rapid, reaching about 7% of injected activity at 10 minutes post-injection and decreasing to 3% after 5 hours. About 30% of the whole brain activity is attributed to striatal uptake. At 48 hours post-injection, approximately 60% of the injected radioactivity is excreted in the urine, with fecal excretion calculated at approximately 14%. Studies of pharmacokinetics have not been conducted in subjects with impaired renal or hepatic function. However, owing to the nature of nuclear imaging and the very small mass dose of ioflupane (< 0.325 microgram per injection), no impact is expected on either efficacy or safety in these patients. Similarly, no safety issues from drug interactions are expected.

Pharmacodynamics: The sponsor used the lack of radioactivity uptake in striatum as a surrogate marker for dopamine neuron degeneration. The sponsor conducted a phase II study to investigate the time course of the uptake of [^{123}I]FP-CIT in various brain regions following intravenous injection to demonstrate differences in striatal uptake of [^{123}I]FP-CIT as determined by SPECT analysis between PD patients and healthy volunteers over a period of 6 hours post-injection. A total of 10 healthy volunteers (male and female 40-70 year old) and 20 patients with Parkinson's disease (male and female 40-70 year old) were studied. SPECT imaging was performed using a Strichman Medical Equipment Gamma Camera. Each subject was injected with 3 mCi of [^{123}I]FP-CIT and imaged at 6 time-points post [^{123}I]FP-CIT injection. The first scan was acquired at 10 minutes post injection and represented a static scan, the remaining five scans were acquired at 1, 2, 3, 4.5 and 6 hours post injection and represented dynamic SPECT scans.

The SPECT endpoints were to determine the accumulation of [^{123}I]FP-CIT in the striatum (target) and OCC (non-target or background) over time in PD patients and healthy volunteer and to determine the ratio of specific to non-specific [^{123}I]FP-CIT binding in the striatum in PD patients compared with healthy volunteers. For the analysis of striatal [^{123}I]FP-CIT binding from the data obtained during static scanning a standard template with regions of interest for the whole striatum, caudate nucleus, putamen and occipital cortex was positioned on the slice with the highest activity. The same template was used to analyze striatal [^{123}I]FP-CIT binding from images obtained during dynamic scanning. Small variations of individual brains required movement of the fixed regions of interest, without changing the size and shape, within the template for optimal fitting. The ratio Specific to non-specific binding of [^{123}I]FP-CIT was calculated as:

	Time Post-injection					
	10 min	1 hr	2 hr	3 hr	4.5 hr	6 hr
Controls (n=10)	0.31±0.14	1.35±0.31	1.93±0.30	2.24±0.32	2.26±0.57	2.10±0.55
Patients (n=20)	0.22±0.17	0.74±0.27	1.02±0.44	0.98±0.53	0.98±0.51	0.95±0.45

Table I. The specific binding of [¹²³I]FP-CIT in healthy volunteers and PD patients in striatum

$$[^{123}\text{I}] \text{FP-CIT specific binding} = (\text{ROI} - \text{OCC}) / \text{OCC}$$

in which ROI represents the mean radioactivity (in SMU) in the region of interest (striatum, caudate nucleus or putamen). The occipital cortex (OCC, radioactivity in SMU) was selected as the background region because the density of dopamine transporters (DAT) is negligible in this area. The binding ratios were also used to calculate putamen:caudate nucleus ratios for the ipsilateral and contra-lateral striatum. In the patients with PD, the contra-lateral striatum was defined as the side opposite to that of initial presentation of motor signs. For the control subjects, contra-lateral was arbitrarily assigned to the left striatum. To estimate the time point of peak specific striatal binding, decay-corrected time activity data for the occipital cortex and striatum were fitted. The time course of [¹²³I]FP-CIT binding in the occipital cortex suggested that the occipital time course of radioactivity is characterized by a rapid uptake and biphasic washout consisting of a fast and slow component.

According to the Table I the healthy volunteers and PD patients showed an increase in radioactivity from 10 min to about 2 hours post-injection. PD patients showed 50% less activity in striatum (3-6 hours postinjection) as compared to healthy volunteers.

Radiation absorbed dose: A phase I study was conducted to investigate biodistribution and excretion characteristics of [¹²³I]FP-CIT in the whole body, and various organs as well as in blood and urine samples during the 48 hour period following intravenous injection containing approximately 111 MBq (3 mCi), and to calculate absorbed radiation dose estimates. Using the Simulation Analysis and Modeling (SAAM) software, the time activity curves for these organs, blood and urine were fitted to a multi-compartmental model. Source organ residence times were determined from integration of the time activity curves from the best fit obtained in the compartment model. Residence times were then used to determine target organ radiation dose using the MIRD methodology for the healthy volunteer, and the MIRDOSE 3.1 software package which assumes urinary bladder emptying at 4.8 hour intervals.

Highest levels of radioactivity were measured in the lungs, liver and brain. The lungs showed the widest (inter-subject) variation in initial uptake and in residence times. Brain uptake was approximately 7% of the %IA, with 30% of this concentrated in the striatum. Radiation dose estimates generated were similar to those previously reported in the literature, confirming an average effective dose equivalent of 0.024 mSv/MBq. This amounted to 2.66 mSv per 111 MBq (3 mCi) and 4.04 mSv for 185 MBq administered which falls well within the World Health Organization category II limits for acceptable risk to healthy volunteers and 50 mSv allowed for occupational workers. It is therefore, acceptable from radiation safety perspective.

Drug-drug interaction: No drug-drug interaction studies were conducted by the sponsor to study the effect of drugs that may influence the expression DAT and SERT (serotonin transporters) on the uptake of ¹²³I-FP-CIT on the striatal uptake. However, based on the mechanism of action, several drugs that bind to dopamine transporter can potentially block or reverse DaTSCAN binding. A literature report shows that preclinical and clinical studies have shown a decrease in striatal binding of 30-50% on patients with methamphetamine or d-amphetamine (appetite suppressant). Similarly, bupropion (an antidepressant and a smoking cessation agent) has been shown to cause a 20% decrease in striatal binding in depressed patients. It is therefore recommended that patients avoid these drugs.

Question Based Review

2.1. General Attributes of the drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

There was no IND filed for this specific submission. The sponsor has used the clinical and clinical pharmacology data from its European submission for this application. A Type C meeting was held on January 31, 2008 with the FDA/Division of Medical Imaging review team for the purposes of discussing GE Healthcare's plan to pursue US registration of DaTSCAN with existing scientific information and to obtain feedback on the nonclinical and technical documentation to be submitted in the NDA. As a result of this meeting, FDA advised GE Healthcare to request a formal Pre-NDA meeting to outline which studies will be submitted to support the qualification of DaTSCAN as a measure of "loss of functional nigrostriatal dopaminergic neurons."

On August 20, 2008, a Type B Pre-NDA meeting was held with FDA to gain concurrence that the primary safety and efficacy data from the principal and supportive clinical studies are adequate to support the proposed detection indication. Following the discussion, the FDA agreed the existing clinical data may be sufficient to support US registration and recommended GE Healthcare proceed to filing the NDA.

DaTSCAN is currently licensed in 32 countries in Europe for a different indication, namely use in the diagnosis of subjects with clinically uncertain Parkinson's Syndrome (PS) to help differentiate them from subjects with essential tremor (ET), and for use in the diagnosis of subjects with clinically uncertain dementia with Lewy bodies (DLB) to help differentiate them from subjects with other types of dementia, AD in particular. The principal data from the European clinical development program have been re-analyzed and re-reported for the US NDA submission to support the proposed detection indication.

2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to the clinical pharmacology of the drug?

DaTSCAN (Ioflupane I-123 Injection) is delivered to the end user as a ready to inject solution containing 2 mCi ¹²³I per mL at reference. The drug product is presented as a sterile solution in ethanolic (5% v/v) sodium acetate (b) (4) for intravenous injection. Vials contain a total of 2.5 mL. The composition in the unit dose vial is summarized in Table II. The chemical structure of [¹²³I]ioflupane is shown in figure I.

Table II. Composition of DaTSCAN (Ioflupane 123I injection).

Ingredient	Amount	Function	Standard
Active Ingredient			
[¹²³ I]ioflupane	74 MBq/mL (2 mCi/mL)* at reference time	Drug Substance	Internal
Other Ingredients			
ioflupane	(b) (4)	(b) (4)	Internal
Ethanol	0.05 mL/mL	(b) (4)	USP
Sodium Acetate	(b) (4)	(b) (4)	Internal
(b) (4)			

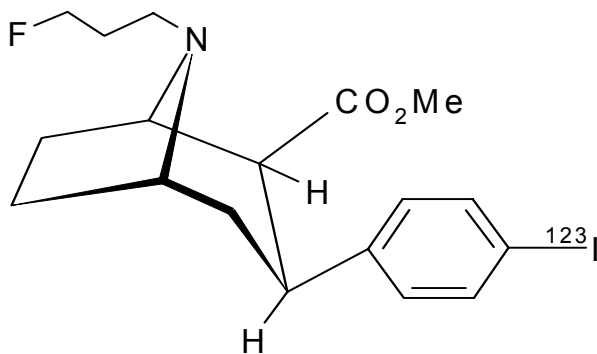


Figure I. Chemical structure of [¹²³I]ioflupane or [¹²³I]FP-CIT

There are no formulation related issues.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication?

¹²³I-FP-CIT (DaTSCAN) is proposed to be indicated for “detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.”

Since the pharmacology of the drug is one of the most important factor for its pharmacodynamic action, a discussion of pre-clinical pharmacology is ensued here.

In vitro studies using various radiolabeled ioflupane show that it binds with high affinity to the dopamine transporter (DaT). FP-CIT binds selectively DaT over the serotonin transporter (SERT) and the norepinephrine transporter (NET). Autoradiographic studies with slices of human brain have shown that ioflupane binds selectively to the striata, which are DaT-rich nuclei in the brain. The striatal binding can be displaced with other compounds known to have strong affinity for the DaT, confirming that ioflupane is binding specifically to the DaT. *In vivo* studies in healthy animals have shown that ioflupane binds selectively to the striata. Such binding can be blocked or reversed by the addition of other compounds which have a high affinity for DaT, again showing that ioflupane is binding specifically to the DaT.

Binding affinity of FP-CIT to selected recombinant human receptors and transporters:

FP-CIT inhibited binding at the human recombinant DaT with a K_i of 623 pM and an IC_{50} of 701 pM, a 5-fold greater affinity than previously shown for the DaT in the rat striatum. In this human recombinant study, FP-CIT shows 3- to 4-fold selectivity for the DaT over the SERT (Table III).

Table III. Binding affinity of FP-CIT to selected recombinant human transporters.

Target	% Inhibition (at conc)	IC_{50}	Ratio of target:DA transport IC_{50}	K_i	Ratio of target: DA transport K_i
DaT	52(1 nM)	701 pM	1	623 pM	1
Adrenergic NET	75 (1 μ M)	229 nM	327	73 nM	117
SERT	79 (10 nM)	2.9 nM	4.14	1.9 nM	3.05

Selectivity over the adrenergic NET was also slightly greater in the human recombinant studies (between 100- and 230-fold). Overall these studies show that FP-CIT has high affinity for the DaT (0.6 nM for the human dopamine recombinant transporter) and against human targets, has a 3- to 4-fold selectivity for the DaT over the SERT. To extend the *in vitro* observations in animal preparations, a whole hemisphere macro autoradiography of post-mortem human brains was used to study the regional binding characteristics of [125 I]FP-CIT along with [125 I] β -CIT and [125 I] β -CIT-FE (other DAT binding structural analogs). The brains used were obtained at clinical autopsy from 3 subjects (53, 54 and 59 years of age). The cause of death in each case was heart failure and the brains were used between 15 hours and 20 hours of death. The cryosections were exposed to solutions of the radioligands for 60 minutes at room temperature followed by washing. In competition experiments the competing substance was added to the incubation fluid.

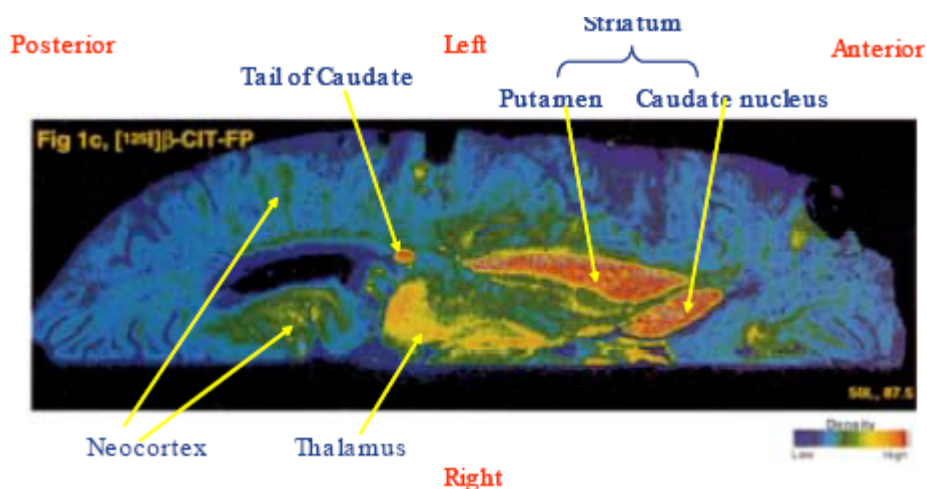


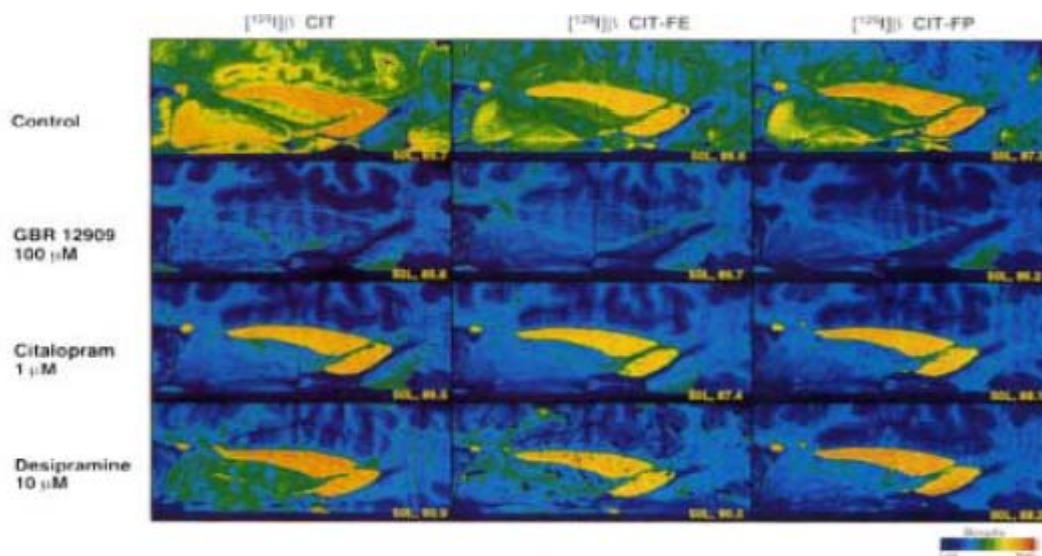
Figure II. Binding of [125 I]β-CIT-FP to striatum in a post-mortem PD human brain

The whole hemisphere autoradiograms (Figure II) for [125 I]β-CIT-FP showed dense labeling of the caudate nucleus and putamen that is consistent with the suggestion that it binds to the DaT. The images also showed, to varying extent, labeling of neocortex and thalamus. Labeling of the DaT in the striatum (caudate nucleus and putamen) was intense and homogeneous. The ratio of striatum to neocortex for [125 I]FP-CIT ([125 I]β-CIT-FP in Figure II was 3.9 ± 0.47 and striatum to thalamus was 2.7 ± 0.44 .

To study the specificity of the binding of the radioligand, competition studies were performed with the DaT inhibitor GBR 12909, the SERT inhibitor citalopram and the NET inhibitor desipramine. Citalopram (included in the incubation solution at a concentration of 1 μ M) reduced binding in the neocortex and thalamus with only minor effects in the striatum. This indicates that the binding in the cortex and thalamus is mainly to the SERT. Desipramine (10 μ M) showed no effect on the level of striatal binding of the radiolabeled analogs, but reduced extrastriatal binding by 60 to 85%. The binding of [125 I]β-CIT-FP and other two analogs to the striatum was blocked in the presence of high concentrations of GBR 12909 (100 μ M), indicating selectivity of binding for the pre-synaptic DaT rather than post-synaptic DA receptors (Figure III). The density of the DaT in the human neocortex as well as in other extrastriatal areas is much lower than in the basal ganglia. The density of the SERT is moderately high in, for example, hypothalamus, thalamus and hippocampus, but is reported to be low in human neocortex. [125 I]β-CIT (an analogous compound) labels sites in most of these regions, including neocortex, whereas [125 I]FP-CIT showed less binding to the extrastriatal regions. The difference is due to the lower affinity for the SERT of [125 I]FP-CIT than of the original compound. It can be therefore conclude that all in vitro data from a variety of preparations indicate that FP-CIT is a compound with a high affinity, and some selectivity, for the DaT.

This selectivity, taken together with relative regional transporter densities, indicates that a high degree of contrast between DaT-rich and -deficient regions would be achievable in normal individuals such that radiolabeled FP-CIT would be a marker of functional dopaminergic neuronal density in the striatum.

Figure III. Specificity of binding to human postmortem brain with different inhibitors.



2.1.4. What are the proposed dosage(s) and route(s) of administration for adults?

The proposed human dose is 3-5 mCi intravenous injection. The dose appeared reasonable from the efficacy standpoint as it provides high target to non-target (striatum to thalamus) ratio. From safety perspective also, the dose is low as it give a low radiation absorbed dose of about 4 mSv with a maximum dose of 5 mCi which is well below allowed limit of 50 mSv.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

There are two clinical pharmacology studies and four clinical studies conducted for the registration of product in US. Clinical pharmacology study CY96-FP2-CSR was a single centre, open study of an intravenous dopamine transporter ligand, containing 111 MBq (3 mCi) [¹²³I]FP-CIT, in healthy volunteers and patients with Parkinson's disease to examine uptake kinetics in various brain sub regions. Another clinical pharmacology study CY95-FP.I was also a single center, open study of an intravenous injection containing 111 MBq [¹²³I]FP-CIT in healthy volunteers. The objective of the study was to investigate biodistribution and excretion characteristics of [¹²³I]FP-CIT in the whole body, and various organs as well as in blood and urine samples during the 48 hour period following intravenous injection containing approximately 111 MBq, and to calculate absorbed radiation dose estimates. The sponsor has conducted four open-label, non-randomized clinical studies, phase III studies (Study 301, 304, 003 multicenter studies), and Walker Study to assess the diagnostic performance and safety of Datscan in subjects with dementia and/or movement disorders. The primary objectives of these studies as presented in the revised U.S. study reports were to determine the sensitivity and specificity of visual interpretations of Datscan SPECT images in detecting or excluding a striatal dopaminergic

deficit (SDD). Visual assessments of Datscan images were compared to the clinical diagnosis (SOT) to determine sensitivity and specificity. With exception of the Walker study, the sponsor has utilized the clinical diagnosis (SOT) as a surrogate for pathology in order to detect loss of functional nigrostriatal dopaminergic neurons, also known as a SDD. The sponsor does this by assuming presence of a SDD in subjects diagnosed with any of the Parkinsonian syndromes (IPD, PSP, MSA) and DLB, and assuming absence of a SDD in subjects clinically diagnosed with ET, AD and healthy volunteers. There were no clinical pharmacology studies conducted to support dosing or dosing claims. The dose (3-5 mCi) was used in clinical trials based on the clinical research experience.

2.2.2 What is the basis for selecting the response endpoints, i.e, clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The applicant conducted a Phase II clinical studies to investigate the time course of brain uptake of ^{123}I -FP-CIT in healthy volunteers and Parkinson's Disease patients over a period of six hours. ^{123}I -FP-CIT uptake in striatum (caudate and putamen) is used as a biomarker for the degeneration of neurons. A total of 10 healthy volunteers (male and female 40-70 year old) and 20 patients with Parkinson's disease (male and female 40-70 year old) were studied. SPECT imaging was performed using a Strichman Medical Equipment Gamma Camera. Each subject was injected with 3 mCi of ^{123}I -FP-CIT and imaged at 6 time-points post ^{123}I -FP-CIT injection. The first scan was acquired at 10 minutes post injection and represented a static scan, the remaining five scans were acquired at 1, 2, 3, 4.5 and 6 hours post injection and represented dynamic SPECT scans.

The SPECT endpoints were to determine the accumulation of ^{123}I -FP-CIT in the striatum (target) and OCC (non-target or background) over time in PD patients and healthy volunteer and to determine the ratio of specific to non-specific ^{123}I -FP-CIT binding in the striatum in PD patients compared with healthy volunteers. For the analysis of striatal ^{123}I -FP-CIT binding from the data obtained during static scanning a standard template with regions of interest for the whole striatum, caudate nucleus, putamen and occipital cortex was positioned on the slice with the highest activity. The same template was used to analyze striatal ^{123}I -FP-CIT binding from images obtained during dynamic scanning. Small variations of individual brains required movement of the fixed regions of interest, without changing the size and shape, within the template for optimal fitting. The ratio Specific to non-specific binding of ^{123}I -FP-CIT was calculated as:

$$[^{123}\text{I}]\text{FP-CIT specific binding} = (\text{ROI} - \text{OCC}) / \text{OCC}$$

in which ROI represents the mean radioactivity in the region of interest (striatum, caudate nucleus or putamen). The occipital cortex (OCC, radioactivity in SMU) was selected as the background region because the density of dopamine transporters (DAT) is negligible in this area. The binding ratios were also used to calculate putamen:caudate nucleus ratios for the ipsilateral and contra-lateral striatum. In the patients with PD, the contra-lateral striatum was defined as the side opposite to that of initial presentation of motor signs. For the control subjects, contra-lateral was arbitrarily assigned to the left striatum. To estimate the time point of peak specific striatal binding, decay-corrected time activity data for the occipital cortex and striatum were fitted. The time course of ^{123}I -FP-CIT binding in the occipital cortex suggested that the occipital time course of radioactivity is characterized by a rapid uptake and biphasic washout consisting of a fast and slow component.

According to the Table I (Page 5) the healthy volunteers and PD patients showed an increase in radioactivity from 10 min to about 2 hours post-injection. PD patients showed 50% less activity in striatum (3-6 hours postinjection) as compared to healthy volunteers.

2.2.4 Exposure-response Evaluation

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

No exposure response studies were conducted or studies reported in literature.

2.2.4.2 Does this drug prolong the QT or QTc interval?

It is expected as ¹²³I-loflupane will not have any significant effect on QTc prolongation as it is administered in submicrogram amount.

2.2.5 Pharmacokinetic Characteristics

2.2.5.1 What are the PK characteristics of the drug and its major metabolites?

DaTSCAN is administered intravenously and is therefore completely bioavailable. It is cleared rapidly from the blood after i.v. injection; only 5% of the administered activity remains in whole blood at 5 minutes post-injection. Uptake in the brain is rapid, reaching about 7% of injected activity (IA) at 10 minutes post-injection and decreasing to 3% after 5 hours. About 30% of the whole brain activity is attributed to striatal uptake. At 48 hours post-injection, approximately 60% of the injected radioactivity is excreted in the urine, with fecal excretion calculated at approximately 14%. Studies of pharmacokinetics have not been conducted in subjects with impaired renal or hepatic function. However, owing to the nature of nuclear imaging and the very small mass dose of ioflupane (< 0.325 microgram per vial), no impact is expected on either efficacy or safety in these patients. Similarly, no safety issues from drug interactions are expected.

2.2.5.2. What is the radiation exposure to patients with a procedure of DaTSCAN?

A phase I study was conducted to investigate biodistribution and excretion characteristics of [¹²³I]FP-CIT in the whole body, and various organs as well as in blood and urine samples during the 48 hour period following intravenous injection containing approximately 111 MBq (3 mCi), and to calculate absorbed radiation dose estimates. Using the Simulation Analysis and Modeling (SAAM) software, the time activity curves for these organs, blood and urine were fitted to a multi-compartmental model. Source organ residence times were determined from integration of the time activity curves from the best fit obtained in the compartment model. Residence times were then used to determine target organ radiation dose using the MIRD methodology for the healthy volunteer, and the MIRDose 3.1 software package which assumes urinary bladder emptying at 4.8 hour intervals.

Highest levels of radioactivity were measured in the lungs, liver and brain. The lungs showed the widest (inter-subject) variation in initial uptake and in residence times. Brain uptake was approximately 7% of the %IA, with 30% of this concentrated in the striatum. Radiation dose estimates generated were similar to those previously reported by other workers, confirming an

average effective dose equivalent of 0.024 mSv/MBq. This amounted to 2.66 mSv per 111 MBq (3 mCi) and 4.04 mSv for 185 MBq administered which falls well within the World Health Organization category II limits for acceptable risk to healthy volunteers and 50 mSv allowed for occupational workers. It is therefore, acceptable from radiation safety perspective.

2.3 Intrinsic factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of age, gender, race, weight, height, organ dysfunction has not been studied.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose- exposure and/or response and what is the impact of any differences in exposure on response?

The effect of ^{123}I -ioflupane on drugs, diet, smoking, alcohol use has not been studied. This is acceptable as these factors do not affect substantially the efficacy of ^{123}I -ioflupane imaging.

2.4.2 Drug-Drug Interactions

No drug-drug interaction studies were conducted by the sponsor to study the effect of drugs that may influence the expression DAT and SERT (serotonin transporters) on the uptake of ^{123}I -FP-CIT on the striatal uptake. However, based on the mechanism of action, several drugs that bind to dopamine transporter can potentially block or reverse DaTSCAN binding. The DAT and SERT play important roles in terminating dopaminergic and serotonergic transmission by reuptake of dopamine and serotonin from the synaptic cleft, respectively.

The following information is excerpted from a recent literature review (Jan Booij and Paul Kemp. Eur. J. Nuc. Med Mol Imaging 2008, 35; 424-428).

Effects of CNS Stimulants:

Amphetamines like methamphetamine or dexamphetamine are not only drugs of abuse. For example, d-amphetamine is a frequently prescribed drug as an appetite suppressant or in attention-deficit-hyperactivity-disorder (ADHD) patients. These amphetamines have a relatively low affinity for DATs [K_i in the micromolar range], but maybe more importantly, these drugs are substrates for the DAT and may induce fast internalization of DATs (and thereby reduce the surface expression to bind the FP-CIT). For example, Laruelle and coworkers [Synapse 1993, 13; 295-309] have shown in monkeys that approximately 50% of striatal (3-CIT binding is displaced by amphetamine, maybe by a fast internalization. Moreover, recent DAT SPECT and PET studies have shown that patients on methamphetamine or with a short abstinence period for methamphetamine (less than 6 months) had significantly lower striatal binding ratios than controls, ranging from 20 to 30% [Volkow et al. Am. J. Psychiatry 2001, 158; 377-382; Chou et al. Eur. Neuropsychopharmacol 2007, 17; 46-52]]. Furthermore, several reports have shown that prolonged use of these drugs may have long-lasting effects on the expression of the DAT, although this phenomenon has been debated by the results of studies performed in methamphetamine abusers with protracted abstinence. Nevertheless, acute or recent administration of these drugs will influence [123 I]FP-CIT.

Like amphetamines, the CNS stimulants (nor)ephedrine, pseudoephedrine, and phentermine are structurally similar to methamphetamine and were or are commonly used appetite suppressants. Chronic ephedrine use, in nutritional supplements, has been reported in female weightlifters, and ephedrines are frequently used as an ingredient in widely marketed herbal preparations. Phentermine is sometimes prescribed to induce weight loss. As compared to amphetamine typical clinical doses of phentermine and ephedrines may not release central DA in humans. Ephedrine and pseudoephedrine are also over-the- sympathomimetics to be used as bronchodilators and nasal decongestants, respectively. Unfortunately, the influence of these drugs on DAT imaging has not been studied. However, taking all data together, we could not exclude an effect of these drugs on DAT studies, particularly when used as tablets. However, it is unlikely that ephedrine-like drugs used as bronchodilators or nasal decongestants will significantly influence central DAT imaging because the plasma concentrations will be too low.

Effects of Analgesics:

Opioids can activate different subtype. Activation of opioid receptors may induce changes in striatal DAT densities in rats. It cannot be excluded that opiates influence binding of [123 I]FP-CIT imaging to DAT.

Effects of Antidepressants:

Bupropion is frequently used as an antidepressant or as an antismoking agent. Several reports show that bupropion blocks DAT in vivo. A recent DAT SPECT study showed that after 4 weeks of bupropion in nine depressed patients, a 20% decrease in striatal DAT binding was observed.

2.4 General Biopharmaceutics:

Not applicable

3.0. Detail Labeling Recommendations:

The following recommendations are made for the clinical pharmacology sections.

12.1 Mechanism of Action

The active drug substance in Datscan is iodine-123- 2-carbomethoxy-3-(4-iodophenyl)-N-(3-fluoropropyl)nortropane or I 123 ioflupane. In vitro, ioflupane binds reversibly to the human recombinant dopamine transporter (DaT) with a high affinity ($K_i = 0.62$ nM; $IC_{50} = 0.71$ nM). Autoradiography of post-mortem human brain slices exposed to radiolabeled ioflupane shows that it concentrates in striatum (caudate nucleus and putamen). The specificity of the binding of the I 125 ioflupane to dopamine transporter was demonstrated by competition studies with the DaT inhibitor GBR 12909 (a dopamine reuptake inhibitor), the SERT inhibitor citalopram, and the NET inhibitor desipramine in post-mortem human brain slices exposed to radiolabeled ioflupane. Citalopram reduced binding in the neocortex and thalamus with only minor effects in the striatum. This indicated that the binding in the cortex and thalamus is mainly to the SERT. Desipramine showed no effect on the level of striatal binding of I 125 ioflupane, but reduced extrastriatal binding by 60 to 85%. The binding of I 125 ioflupane to the striatum was abolished in the presence of high concentrations of GBR 12909, indicating selectivity of binding for the pre-synaptic DaT rather than post-synaptic DA receptors.

7. Drug Interaction

Based upon the mechanism of action, the following drugs could interfere with Datscan imaging: amphetamine, benztropine, bupropion, cocaine, mazindol, methylphenidate, phentermine and sertraline. Clinical studies have shown a decrease in striatal binding of 30-50% on patients with methamphetamine or d-amphetamine (appetite suppressant) (Am. J. Psychiatry 2001, 158, 377-382; Neuropsychopharmacol. 2007, 17, 46-52).

Bupropion (an antidepressant and a smoking cessation agent) has been shown to cause a 20% decrease in striatal binding in depressed patients (J. Affect Disorder 2005, 89, 115-123).

Single dose of 20 mg Citalopram (SERT blocking ligand) increases striatal binding ratio to 20% (J. Nucl. Med. 2007, 48, 359-366).

The effect of these drugs on the uptake of I 123 ioflupane can lead to false positive or false negative results. Caution should be exercised in interpreting images of patients on dopamine transporter binding or serotonin transporter binding drugs.

4.0 APPENDICES:

4.1 Proposed Package Insert (Original and Annotated)

14 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page



4.2 INDIVIDUAL STUDY REVIEW:

STUDY CY96-FP2-CSR:

This was a single centre, open study of an intravenous dopamine transporter ligand, containing 111 MBq (3 mCi) [123 I]FP-CIT, in healthy volunteers and patients with Parkinson's disease to examine uptake kinetics in various brain sub regions and safety.

Study Objectives:

The objectives of this study were:

1. To investigate the time course of the uptake of [123 I]FP-CIT in various brain regions following intravenous injection in order to determine the optimal time post-injection for in vivo DA transporter DAT) imaging. For this purpose SPECT studies were performed at the level of the basal ganglia up to 6 hours postinjection. The optimum time of acquisition has been defined as the time at which specific radioactivity in the striatum is at a stable level.
2. To demonstrate differences in striatal uptake of [123 I]FP-CIT as determined by SPECT analysis between Parkinson's disease patients and healthy volunteers over a period of 6 hours post-injection.
3. To assess safety and tolerability parameters following [123 I]FP-CIT administration as follows: analysis of blood (hematology and biochemistry) and urine (biochemistry) assessment of vital signs (blood pressure, heart rate and temperature), and ECG. recording of adverse events.

No. of Subjects: A total of 30 subjects studied 10 healthy volunteers (male and female 40-70 year old) and 20 with Parkinson's disease (male and female 40-70 year old). SPECT imaging was performed using a Strichman Medical Equipment 810X consisting of 12 individual crystals, each equipped with a focusing collimator. Each subject was imaged at 6 time-points post [123 I]FP-CIT injection. The first scan was acquired at 10 minutes post injection and represented a static scan, the remaining five scans were acquired at 1, 2, 3, 4.5 and 6 hours post injection and represented dynamic SPECT scans. Routine laboratory assessments including hematology, biochemistry and urinalysis were conducted at baseline screening, 1 hour prior to [123 I]FP-CIT injection, and at 6 hours and 24- 72 hours post-injection. All laboratory analyses were conducted and reported by the local laboratory at the (b) (4). Each laboratory parameter was reported in reference to normal values provided by the laboratory. Vital signs (blood pressure and heart rate), and temperature were assessed at baseline screening, 1 hour prior to injection, and 3 hours and 24-72 hours post-injection using standard methods. Standard 12 lead electrocardiogram (ECG) recordings were performed for all subjects over a 20 minute period 1 hour prior to [123 I]FP-CIT injection, and at 3.5 hours post [123 I]FP-CIT injection. Adverse events were assessed throughout the study.

Statistical Methods:

Individual data for each brain area obtained by imaging were corrected for radioactive decay and averaged. Possible time trends in ratios of uptake in brain regions were determined by repeated non-parametric analysis of variance (ANOVA). Differences in groups were analysed with the Wilcoxon's two-sample rank sum test. In the case of multiple comparisons the Bonferroni correction method was used. In all statistical analyses, probability values of <0.05 were considered significant. There was no formal analysis of safety data planned or conducted for this study.

Study Design:

This study was designed as a single-centre, parallel group, open, comparative, nonrandomised, clinical study to investigate the uptake kinetics and safety of a single intravenous injection of test product [^{123}I]FP-CIT containing approximately 111 MBq (3 mCi) in Parkinson's disease patients and healthy volunteers. A total of 30 subjects (10 healthy volunteers and 20 Parkinson's patients) aged between 40-70 years with an age appropriate health condition were planned, screened, and recruited into this study. In order to participate in this study subjects were required to present to the study site on a maximum of 3 occasions.

Efficacy Measurement:

SPECT imaging was performed using a Strichman Medical Equipment 810X (Strichman Medical Equipment Inc., Medfield, Mass., USA), consisting of 12 individual crystals, each equipped with a focusing collimator. Each subject was imaged at 6 time-points post [^{123}I]FP-CIT injection. The first scan, acquired at 10 minutes post injection, represented a static scan and involved multislice SPECT acquisition (starting at and parallel to the orbitomeatal line, 150 seconds per slice; interslice distance 10 mm) to locate the slice demonstrating best visualisation of the striatum. The subsequent 5 scans acquired at 1, 2, 3, 4.5 and 6 hours post injection represented dynamic SPECT scans (8 consecutive acquisitions of 150 seconds per slice) performed at the level of the reference slice defined during the static SPECT scan. The acquisition period for each scan (static and dynamic) was approximately 20 minutes. The energy window was set at 135-190keV. Data acquisition took place in a 128 x 128 matrix. A linear attenuation correction, based on an absorption length of 95nm was applied in all studies. Images were automatically reconstructed with a variable filter, according to the level of counts per slice. The measured concentration of radioactivity was expressed as Strichman Medical Units (SMU's; 1 SMU = 100 Bq/mL, as specified by Strichman Medical Equipment Inc.). The optimum time of acquisition was defined as the time at which the specific radioactivity in the striatum (calculated as total striatal counts minus counts in the occipital cortex) reached its highest value in all subjects. Only 1 out of the 30 subjects recruited into the study was unable to complete all 6 scans in accordance with the protocol. Subject number 26 (PD patient) was unable to perform the 2 hours post [^{123}I]FP-CIT injection scan, and unable to complete the 3 hours post [^{123}I]FP-CIT injection scan due to the development of a severe 'off phase'. The inability of subject 26 to complete all 6 scans in accordance with the protocol represents a protocol deviation. However, this subject has already been classified as a protocol violator as they did not meet all of the PD diagnosis criteria. The subject therefore, remained classified as a protocol violator.

Primary Efficacy variable:

With regard to efficacy, this study is designed to evaluate the brain uptake kinetics of a single i.v. injection of [^{123}I]FP-CIT over a period of approximately 6 hours post injection in 2 subject groups (healthy volunteers and PD patients). The SPECT endpoints of interest were as follows:

- i) Accumulation of [^{123}I]FP-CIT in the striatum and occipital cortex over time in PD patients and healthy volunteers.
- ii) Ratio of specific to non-specific [^{123}I]FP-CIT binding in the striatum in PD patients compared with healthy volunteers.
- iii) Ratio of specific to non-specific [^{123}I]FP-CIT binding in 6 brain regions of interest, (ipsilateral and contralateral striatum, caudate and putamen), in PD patients compared with healthy volunteers.
- iv) Ratio of specific to non-specific [^{123}I]FP-CIT binding in 6 brain regions of interest, in PD patients rated as H&Y 1 (hemi-Parkinson's disease) compared with healthy volunteers.

Efficacy Analysis:

The investigator was responsible for the analyses and reporting of all efficacy data. For the analysis of striatal [¹²³I]FP-CIT binding for data obtained during static scanning a standard template with regions of interest for the whole striatum, caudate nucleus, putamen and occipital cortex was positioned on the slice with the highest activity. The same template was used to analyse striatal [¹²³I]FP-CIT binding from images obtained during dynamic scanning. Small variations of individual brains required movement of the fixed regions of interest, without changing the size and shape, within the template for optimal fitting. Specific to non-specific [¹²³I]FP-CIT binding was calculated as:

$$[^{123}\text{I}]\text{FP-CIT binding} = (\text{ROI} - \text{OCC}) / \text{OCC}$$

in which ROI represents the mean radioactivity (in SMU) in the region of interest (striatum, caudate nucleus or putamen). The occipital cortex (OCC, radioactivity in SMU) was selected as the background region because the density of dopamine transporters (DAT) is negligible in this area. The binding ratios were also used to calculate putamen:caudate nucleus ratios for the ipsilateral and contra-lateral striatum. In the patients with PD, the contra-lateral striatum was defined as the side opposite to that of initial presentation of motor signs. For the control subjects, contra-lateral was arbitrarily assigned to the left striatum. To estimate the time point of peak specific striatal binding, decay-corrected time activity data for the occipital cortex and striatum were fitted. The time course of [¹²³I]FP-CIT binding in the occipital cortex suggested that the occipital time course of radioactivity is characterized by a rapid uptake and biphasic washout consisting of a fast and slow component.

Results:

[¹²³I]FP-CIT time-activity curves for the striatum and occipital cortex of representative control and PD subjects are shown in Figure, together with the calculated specific striatal uptake (i.e. striatal uptake less occipital cortex uptake). Each of the eight data sets collected at each time point are presented. The time to peak specific striatal activity observed in PD patients was found to be faster when compared with that for healthy volunteers but in all cases 95% of the peak specific striatal binding was reached within a period of 3 hours post [¹²³I]FP-CIT injection.

Figure 4. Radioactivity (in SMU) in the striatum (•), occipital cortex (♦) (A) and specific striatal radioactivity (▲) from 0-6 hours post [123 I]FP-CIT injection in a representative (A) healthy volunteer and (B) PD patient.

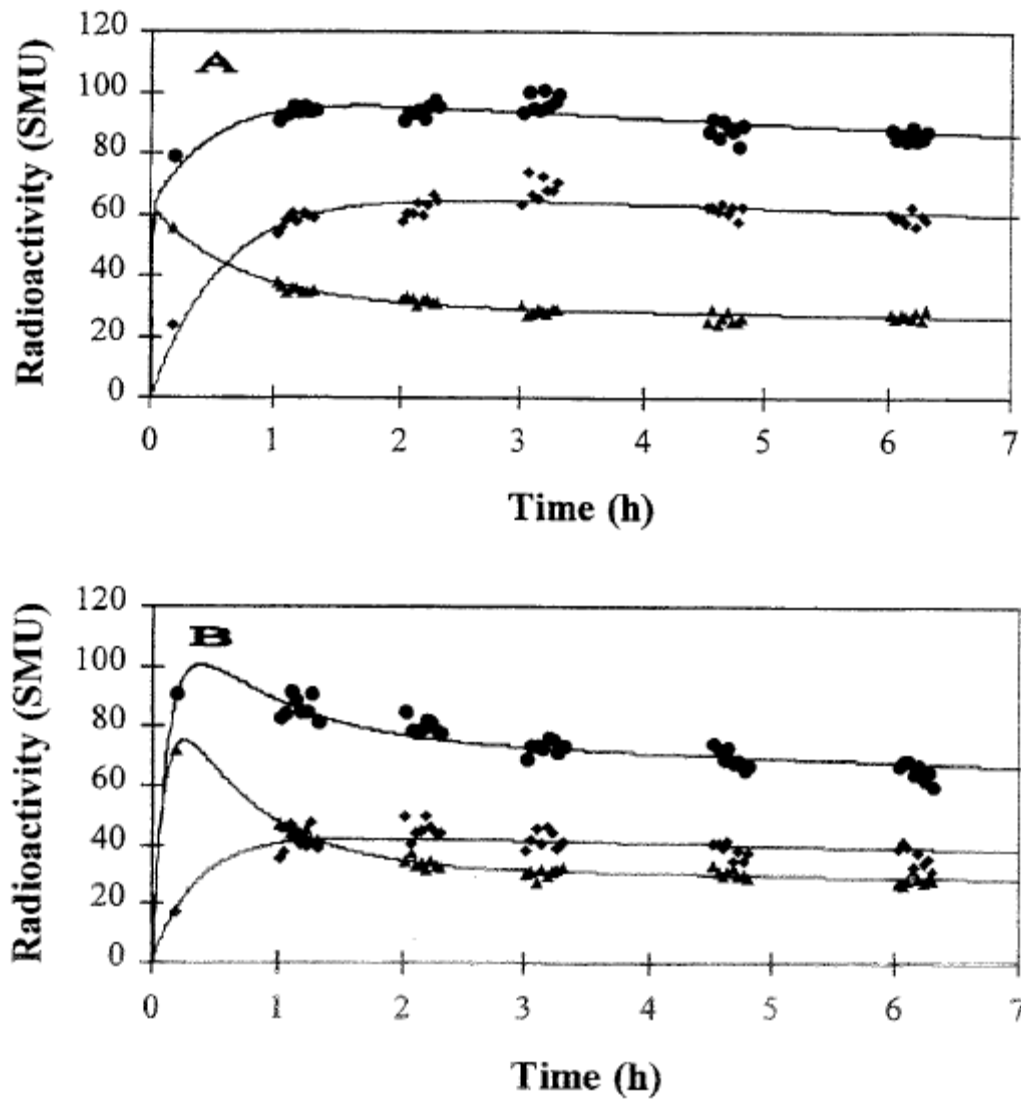


Table IV. [123]FP-CIT binding ratios (specific striatal binding/non-specific binding) in healthy volunteers in PD patients (mean \pm SD)

	Time post-injection					
	10 min	1 h	2 h	3 h	4.5 h	6 h
Controls (n=10)	0.31 \pm 0.14	1.35 \pm 0.31*	1.93 \pm 0.30*	2.24 \pm 0.32*	2.26 \pm 0.57*	2.19 \pm 0.55*
Patients (n=20)	0.22 \pm 0.17	0.74 \pm 0.27*	1.02 \pm 0.44**	0.98 \pm 0.53*	0.98 \pm 0.51*	0.95 \pm 0.45*
Subject 21	0.55	1.32	2.37	2.74	2.82	2.46
Patients (n=19)	0.20 \pm 0.15	0.71 \pm 0.24	0.94 \pm 0.29 ¹	0.89 \pm 0.34	0.89 \pm 0.27	0.87 \pm 0.28

*p<0.01

**n=19

¹n=18 (subject 26 was not imaged at 2h)

Table V. Mean (\pm SD) [123]FP-CIT SPECT measurement in healthy volunteers

	3 h post-injection		4.5 h post-injection		6 h post-injection	
	Controls	Patients	Controls	Patients	Controls	Patients
	(n=10)	(n=18) [§]	(n=10)	(n=18) [§]	(n=10)	(n=18) [§]
Striatum:						
Contralateral	2.23 \pm 0.32	0.80 \pm 0.29*	2.23 \pm 0.61	0.80 \pm 0.22*	2.21 \pm 0.55	0.77 \pm 0.23*
Ipsilateral	2.25 \pm 0.35	1.00 \pm 0.43*	2.30 \pm 0.54	0.97 \pm 0.37*	2.16 \pm 0.57	0.99 \pm 0.39*
Caudate:						
Contralateral	2.57 \pm 0.37	1.20 \pm 0.50*	2.53 \pm 0.55	1.28 \pm 0.40*	2.57 \pm 0.59	1.15 \pm 0.40*
Ipsilateral	2.58 \pm 0.41	1.37 \pm 0.52*	2.70 \pm 0.56	1.36 \pm 0.48*	2.62 \pm 0.59	1.43 \pm 0.51*
Putamen:						
Contralateral	2.23 \pm 0.45	0.67 \pm 0.23*	2.24 \pm 0.77	0.59 \pm 0.18*	2.17 \pm 0.65	0.62 \pm 0.20*
Ipsilateral	2.14 \pm 0.41	0.88 \pm 0.43*	2.20 \pm 0.63	0.84 \pm 0.35*	2.03 \pm 0.67	0.81 \pm 0.35*
Putamen/caudate ratio:						
Contralateral	0.88 \pm 0.19	0.62 \pm 0.25*	0.89 \pm 0.22	0.48 \pm 0.10*	0.85 \pm 0.19	0.58 \pm 0.22*
Ipsilateral	0.84 \pm 0.16	0.63 \pm 0.14*	0.82 \pm 0.18	0.62 \pm 0.12*	0.77 \pm 0.16	0.56 \pm 0.13*

Reviewer's Comments: The ratio of specific (striatum) to non-specific (OCC) [123]FP-CIT binding was significantly lower (50%) in PD patients when compared with healthy volunteers, as early as 3 hour post [123]FP-CIT injection. No significant time trend was found for the ratios of specific to non-specific [123]FPCIT binding in the striatum, caudate, and putamen, between 3 and 6 hours post injection in either patient or control groups. Significantly lower ratios of specific to non-specific [123]FP-CIT binding were found in the PD patient population when compared with healthy volunteers at these times for all six brain regions measured, i.e. ipsilateral and contralateral measurements for the striatum, caudate and putamen. Since the ratios in both control and patient groups are stable between 3 and 6 hours post-injection this provides the most suitable time window for diagnostic imaging. The difference in uptake ratios between the two groups throughout the 3 to 6 hour time window are sufficient to suggest that visual analysis of the SPECT images should provide adequate differential diagnosis.

STUDY CY95-FP.I

Objective:

This was a single center, open study of an intravenous dopamine transporter ligand containing 111 MBq [^{123}I]FP-CIT in healthy volunteers to examine biodistribution, safety and tolerability. The primary objective of the study was to investigate biodistribution and excretion characteristics of [^{123}I]FP-CIT in the whole body, and various organs as well as in blood and urine samples during the 48 hour period following intravenous injection containing approximately 111 MBq, and to calculate absorbed radiation dose estimates. The secondary objective was to assess safety and tolerability parameters at regular time intervals following intravenous injection containing approximately 111 MBq of [^{123}I]FP-CIT.

Total Number of Subjects: There were a total of 12 subjects 6 male and 6 female enrolled in this study.

Criteria for Evaluation:

Whole body transmission and emission scans were performed using a dual headed gamma camera (Siemens Bodyscan). For each volunteer a whole body transmission scan was acquired 1 hour prior to injection of [^{123}I]FP-CIT by placing a flat source containing approximately 370 MBq [^{123}I] on the posterior gamma camera head and reporting counts from the anterior head. Whole body emission scans were performed following [^{123}I]FP-CIT administration. Emission images were obtained at 10 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 24 hours and 48 hours post injection. Acquisition of the emission scans were performed simultaneously in the anterior and posterior view using a standard data acquisition technique. [^{123}I] blood clearance studies were performed on blood samples collected 1 hour prior to [^{123}I]FP-CIT injection and serially at 5 minutes, 15 minutes, 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 24 hours and 48 hours post injection. Three 1 mL aliquots per sample were assessed for radioactivity using an automatic gamma counter. The radioactivity measurements were corrected for physical decay, and the amount of radioactivity in the blood was calculated using formulae based on the volunteer haematocrit values, body weight and height, and were expressed as a percentage of injected activity (%IA) of [^{123}I]FP-CIT.

Routine laboratory assessments including haematology, biochemistry and urinalysis were conducted at baseline screening, 1 hour prior to injection of [^{123}I]FP-CIT, and at 2-4 hours and 48 hours post injection. All laboratory analyses were conducted and reported by the local laboratory at the (b) (4). Each laboratory parameter was reported in reference to normal values provided by the laboratory. Vital signs (blood pressure and heart rate), and temperature were assessed at baseline screening, 1 hour prior to injection, and at 10 minutes, 20 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 24 hours and 48 hours post injection using standard methods. Standard 12 lead electrocardiogram (ECG) and conventional electroencephalogram (EEG) recordings were performed for 6 out of the 12 volunteers recruited for this study. Twenty minute ECG recordings were made at baseline screening and 2 and 5 hours post [^{123}I]FP-CIT injection. EEG recordings were performed for a twenty minute duration at baseline screening and continuously from the time of [^{123}I]FP-CIT injection up to 5 hours post injection.

Adverse events were assessed throughout the study. A tolerability questionnaire was issued to each volunteer for completion 1 hour prior to [123 I]FP-CIT injection, and at 15 minutes, 1 hour, 4 hours, 24 hours, and 48 hours post injection. The questionnaire evaluated volunteer mood, pain at the injection site, itchiness of injection site, loss of function at injection site and quality of sleep using 100mm visual analogue scales.

Statistical Methods:

Region of interest (ROI) analyses were performed using whole body emission scan data for various organs (whole brain, lungs, heart, liver, stomach, spleen, intestines, bladder, thyroid, and striatum). Similarly, ROI analyses for the same organs, as well as an off body region, were performed using whole body transmission scans. A transmission factor reflecting the fraction of counts passing through the organ was calculated for each volunteer by determining the counts/pixel for each organ ROI divided by the counts/pixel for an unattenuated off body region. Attenuation correction of the conjugate emission scans was performed by dividing the geometric mean of the posterior and anterior counts in each ROI by an attenuation factor equal to the square root of the transmission factor.

Time activity curves were generated for specific ROI organs. Using the Simulation Analysis and Modeling (SAAM) software, the time activity curves for these organs, blood and urine were fitted to a multi-compartmental model. Source organ residence times were determined from integration of the time activity curves from the best fit obtained in the compartment model. Residence times were then used to determine target organ radiation dose using the MIRD methodology for the healthy volunteer, and the MIRDOSE 3.1 software package which assumes urinary bladder emptying at 4.8 hour intervals. Formal statistical analyses of 123 I blood and urine clearance data were not performed. There was no formal analysis of safety and tolerability data.

Summary Conclusions:

[123 I]FP-CIT was shown to be well tolerated with no adverse events reported or observed. Clearance of 123 I activity from the blood was rapid with approximately 95% of the %IA cleared after 5 minutes, and approximately 98% cleared after 15 minutes post [123 I]FP-CIT injection. Subsequent to this time blood activity remained stable beyond 5 hours post injection, and steadily decreased to approximately 1% of the injected dose within 48 hours post injection. Elimination from the whole body via voided urine was approximately 60% of %IA at 48 hours post injection. Other excreta were not measured.

Highest levels of radioactivity were measured in the lungs, liver and brain. The lungs showed the widest (inter-subject) variation in initial uptake and in residence times. Brain uptake was approximately 7% of the %IA, with 30% of this concentrated in the striatum. Radiation dose estimates generated were similar to those previously reported by other workers, confirming an average effective dose equivalent of 0.024 mSv/MBq. This amounted to 2.66 mSv per 111 MBq administered which falls well within the World Health Organisation category II limits for acceptable risk to healthy volunteers. In summary, therefore, the biodistribution of in this study involving 12 healthy volunteers demonstrated safe, high and stable brain uptake with dosimetry favourable for clinical SPECT imaging.

RATIONALE FOR DOSE SELECTION:

[123 I]FP-CIT has been demonstrated to be a safe DAT marker in pre-clinical studies. In addition, 111 MBq of [123 I]FP-CIT has been shown to represent sufficient activity, when injected i.v, for performing whole body imaging and SPECT image analysis (from literature), the latter being of particular importance to the future development of the test product.

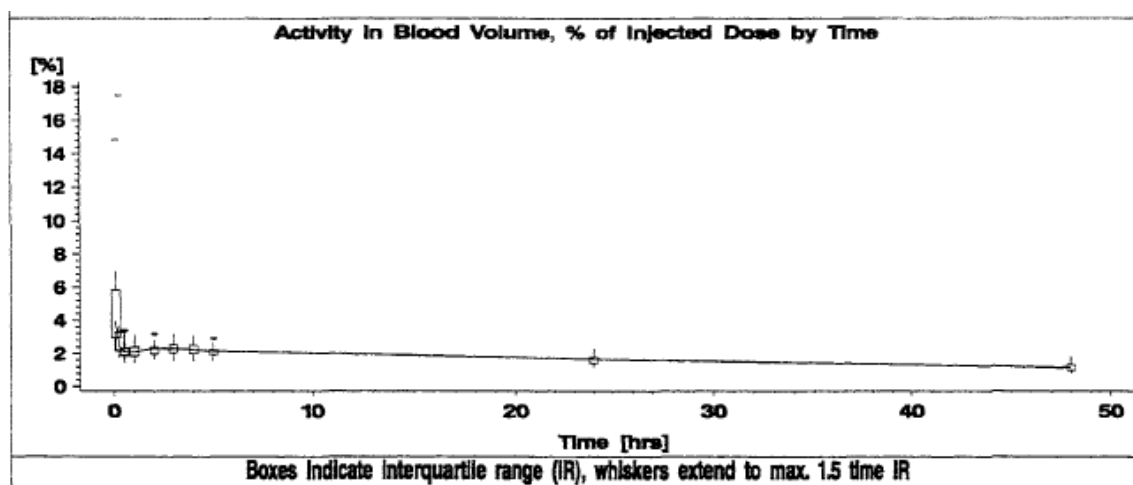
Furthermore, given the low dose of activity, and the high brain washout rate the anticipated safety profile of the test product was considered satisfactory for use in healthy volunteers. This was further supported by the absorbed dose calculation of 4.77 mSv derived from the somatic effective dose equivalent of 0.043 mSv/MBq estimated in healthy volunteers thus satisfying the WHO category II criteria for healthy volunteers. Both the effective dose equivalent and absorbed dose for 111 MBq [^{123}I]FP-CIT were calculated as part of the biodistribution evaluation conducted in this study. In addition, the small amount of non-radioactive FP-CIT present in the test product was not expected to exert any pharmacological effect. Nevertheless, as FP-CIT represents a structural analogue of cocaine, post [^{123}I]FP-CIT injection EEG and ECG recordings were conducted in a representative half of the volunteer population and compared against baseline recordings as a means to examine the appearance of any potential toxic events.

Blood Clearance:

Blood clearance was shown to be rapid. Initial blood sampling at 5 minutes post [^{123}I]FP-CIT administration revealed a mean activity of 4.84 ± 2.94 MBq/BV, representing 4.99 ± 3.43 %IA (n=12, mean \pm SD). At 30 minutes post [^{123}I]FP-CIT administration the mean activity had reduced to 2.13 ± 0.55 MBq/BV representing 2.14 ± 0.51 %IA (n=12). From 30 minutes post [^{123}I]FP-CIT administration the level of activity in the whole blood volume was maintained up to a minimum of 5 hours post injection. Further blood sampling at 24 and 48 hours post [^{123}I]FP-CIT administration demonstrated a gradual reduction in residual activity resulting in a mean activity of 1.20 ± 0.34 MBq/BV representing 1.20 ± 0.30 %IA at 48 hours post injection. Summary data for the 48 hour period post [^{123}I]FP-CIT administration are presented in Table 2 and displayed in Figure 3a. The high level of variability observed over the initial 15 minute post injection sampling period can be attributed to 1 volunteer (subject number 3) who received [^{123}I]FP-CIT via the cannula introduced specifically for the purpose of blood sampling. This error resulted in artificially elevated blood counts at 5 and 15 minutes post injection. This volunteer was therefore, removed from the dataset and the mean values for 1231 blood clearance recalculated using a sample size n=11 Recalculated summary data (n=11) are presented in Figure 3b. All subsequent biodistribution analyses involving blood volume and 1231 blood clearance rates, i.e. radiation dose estimates and dosimetry, were conducted using a sample size n=12.

Table VI. [^{123}I]FP-CIT blood clearance

	5	15	30	1	2	3	4	5	24	48
	min.	min.	min.	hour	hours	hours	hours	hours	hours	hours
Counts [cpm/ml]										
Mean	32708	24129	14068	13964	15039	15330	15084	14424	11027	7921
N	12	12	12	12	12	12	12	12	12	12
Missing	0	0	0	0	0	0	0	0	0	0
SD	19737.1	25214.9	1298.0	1063.3	1661.5	2058.5	2303.9	2348.7	1438.8	1040.5
Minimum	14122	12354	12270	12838	13568	13631	13480	12522	8301	5891
Maximum	87772	103637	16593	16956	19404	20806	21346	21141	13914	9335
Activity [MBq/BV]										
Mean	4.84	3.62	2.13	2.11	2.26	2.30	2.25	2.14	1.66	1.20
N	12	12	12	12	12	12	12	12	12	12
Missing	0	0	0	0	0	0	0	0	0	0
SD	2.94	3.76	0.55	0.47	0.50	0.49	0.43	0.38	0.42	0.34
Minimum	2.1	1.7	1.4	1.4	1.6	1.5	1.5	1.5	1.1	0.8
Maximum	13.0	15.4	3.2	2.9	3.0	3.0	2.9	2.8	2.4	1.8
Percentage of Injected Activity [%IA]										
Mean	4.99	3.77	2.14	2.12	2.27	2.31	2.27	2.16	1.66	1.20
N	12	12	12	12	12	12	12	12	12	12
Missing	0	0	0	0	0	0	0	0	0	0
SD	3.43	4.36	0.51	0.45	0.42	0.46	0.44	0.36	0.34	0.30
Minimum	2.2	1.7	1.4	1.5	1.6	1.5	1.5	1.5	1.2	0.8
Maximum	14.8	17.5	3.4	3.1	3.2	3.2	3.1	2.9	2.3	1.8



Region of Interest Brain:

The uptake and retention in the whole brain is shown below:

Table VII. Whole brain radioactivity of [I-123]FP-CIT

	10	1	2	3	4	5	24	48
	minutes	hour	hours	hours	hours	hours	hours	hours
Mean	6.84	4.22	3.53	3.18	3.07	3.00	2.38	1.58
N	12	12	12	12	12	12	12	12
SD	2.09	0.84	0.74	0.59	0.53	0.52	0.59	0.38
Maximum	10.9	6.14	5.06	4.16	3.76	3.73	3.21	2.15

Relatively low levels of I-123 uptake was observed in striatum (2.02 ± 0.75 % injected activity; $n=12$). Over subsequent 5 hours period there was a rapid decline in uptake 0.99 ± 0.23 % injected activity at 3 hours post injection and 0.92 ± 0.24 % injected activity at 5 hrs post-injection. Thereafter, the uptake of [123 I]FP-CIT gradually reduced resulting in means of 0.75 ± 0.2 % injected activity at 24 hrs and 0.46 ± 0.14 % IA at 48 hours post-injection.

Most of the administered radioactivity was eliminated by renal system. The mean urinary excretion at 48 hours post-injection was 60% of the administered activity, whereas mean predicted % of administered activity excreted in feces was 14% at 48 hours post-injection.

The radiation absorbed dose estimates were calculated for each subject independently and then averaged. The organs that received the highest absorbed doses were urinary bladder wall (0.054 mGy/MBq), followed by lungs (0.043 mGy/MBq), lower large intestines (0.042 mGy/MBq) and upper large intestines (0.038 mGy/MBq). The mean effective dose for the normal adult was estimated to be 0.024 mSv/MBq. The self-dose to striatum was estimated to be 0.23 mGy/MBq.

Table VIII. Radiation absorbed doses (mGy/MBq) for various organs

Target Organ	Absorbed Dose mGy/MBq (n=12)	SD
Adrenals	1.31 E-02	1.00E-03
Brain	1.81 E-02	5.04E-03
Breasts	8.00E-03	7.20E-04
Gallbladder wall	2.57E-02	1.49E-03
LLI Wall	4.24E-02	4.37E-03
Small Intestine	2.06E-02	1.37E-03
Stomach	1.14E-02	9.12E-04
ULI Wall	3.81 E-02	3.87E-03
Heart Wall	1.31E-02	1.16E-03
Kidneys	1.11 E-02	9.33E-04
Liver	2.83E-02	4.22E-03
Lungs	4.25E-02	1.25E-02
Muscle	9.64E-03	7.33E-04
Ovaries	1.70E-02	8.41E-04
Pancreas	1.32E-02	1.02E-03
Red Marrow	9.77E-03	7.59E-04
Bone Surfaces	1.74E-02	1.64E-03
Skin	6.27E-03	6.31 E-04
Spleen	1.06E-02	9.43E-04
Testes	8.79E-03	7.56E-04
Thymus	1.03E-02	9.43E-04
Thyroid *	9.21 E-03	1.03E-03
Urinary Bladder Wall	5.35E-02	8.10E-03
Uterus	1.63E-02	5.73E-04
Total Body	1.15E-02	7.80E-04
Effective Dose Equivalent (mSv/MBq)	2.38E-02	1.52E-03
Effective Dose (mSv/MBq)	2.35E-02	1.52E-03

Reviewer's Comments:

[¹²³I]FP-CIT has been studied extensively as DAT marker in pre-clinical studies including non-human primates. In addition, there is a load of information from research articles published in the literature on structurally similar compounds such as [¹²³I]beta-CIT regarding dose and pharmacokinetics. 111 MBq of [¹²³I]FP-CIT has been shown to represent sufficient activity, when injected i.v, for performing whole body imaging and SPECT image analysis based on literature reports. Furthermore, given the low dose of radioactivity, and the high brain washout rate the anticipated safety profile of the test product was considered satisfactory for use in healthy volunteers. Also the radiation dosimetry study supported a low total absorbed dose of about 4.3 mSv derived from .0235 mSv/MBq effective dose in healthy volunteers thus satisfying the WHO category II criteria for healthy volunteers. In addition, the small amount (<0.325 µg) of non-radioactive FP-CIT present in the test product was not expected to exert any pharmacological effect.

4.3 Consult Reviews (including Pharmacometric Reviews): N/A

4.4 Cover Sheet and OCP Filing/Review Form

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
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NDA 22454	ORIG 1	GE HEALTHCARE INC	DA TSCAN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTY S JOHN
08/28/2009

YOUNG M CHOI
08/31/2009